Dapsone in a Large Tertiary Center: Outdated Therapeutic Option or Timeless Agent?

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Abstract: BACKGROUND The ancient drug dapsone has antimicrobial and anti-inflammatory features. In dermatology, dapsone is primarily used for neutrophil-dominant skin diseases. However, real-life data assessing the long-term efficacy of dapsone across multiple dermatological diseases is missing. -Objectives: To determine the efficacy and safety of dapsone in patients with inflammatory skin diseases treated at the Department of Dermatology of the University Hospital Zurich. METHODS The hospital database was searched for patients treated with dapsone in the last 20 years (from January 1, 1998, to December 31, 2017). Overall, 175 patients were included in our study. RESULTS Thirty-four patients received dapsone for eosinophilic dermatoses, 82 for neutrophilic dermatoses and 59 for other dermatoses. After 3 months, 8% of all patients reached complete remission, 40.6% showed improvement, 30.3% had stable disease, and only 9.1% had disease progression. Final treatment evaluation revealed complete response in 13.2%, disease improvement in 47.4%, stable disease in 25.7% and disease progression in only 12.0%. Patients who showed remission or improvement after 3 months were significantly older than patients with stable or progressive disease. In addition, remission after 3 months was associated with a significantly lower dose of dapsone compared to improvement only. Hemolysis was the most common adverse event (21.7%). CONCLUSIONS Our data show that dapsone is a valid treatment option in various dermatological diseases, leading to a favorable response in the vast majority of patients. In addition, it is well tolerated, safe and inexpensive. Randomized, controlled trials are needed to further elucidate the role of this high-potential drug.

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Keywords
Dapsone · Neutrophilic dermatoses · Eosinophilic dermatoses · Efficacy · Drug safety

Abstract
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Introduction

The sulfone dapsone (4,4'-diaminodiphenylsulfone) is an aniline derivative and was first synthesized in 1908, but its medical use was only later discovered in 1937 [1]. In an experimental model, it was efficient to treat strepto-

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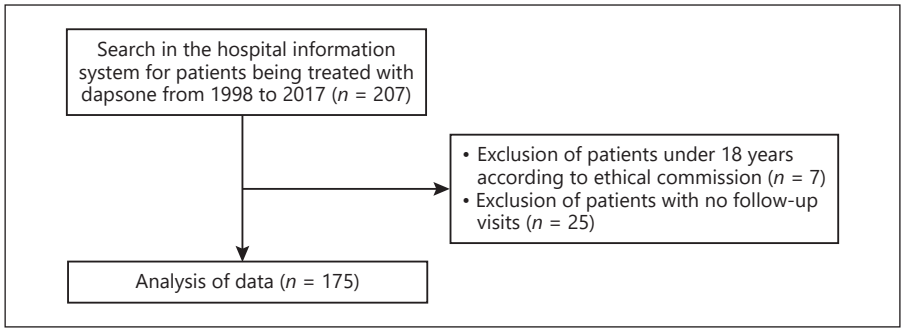

Fig. 1. Flow chart of the Methods: patient selection for analysis. Participant inclusion and exclusion flow diagram. Exclusion criteria encompassed age younger than 18 years.

coccal infections in mice [2, 3] and later on in the treatment of sexually transmitted infections, such as gonorrhea [1]. Over time, it gained significance as a steroid-sparing treatment option for several skin diseases, such as bullous pemphigoid, linear IgA dermatosis and dermatitis herpetiformis [2].

The chemical structure of dapsone encompasses a sulfur atom, covalently bound to 2 carbon atoms. Upon oral intake, it enters the enterohepatic circulation and is absorbed in the gut with bioavailability reaching 86%. Dapsone is eliminated primarily as metabolites in the urine, while only a small amount is eliminated in the feces [1, 4]. Hepatic metabolization occurs through acetylation and hydroxylation [1]. Dapsone passes the brain-blood barrier as well as the placenta and can be found in breast milk [5, 6], leading to fetal cyanosis [7].

Dapsone has antimicrobial, antiprotozoal and anti-inflammatory properties [8]. It inhibits the synthesis of dihydrofolic acid [1], thus inhibiting neutrophil influx (chemotaxis) and tissue injury [9], while suppressing secretion of inflammatory cytokines [10]. Accordingly, in dermatology, dapsone is classically used for skin diseases with increased neutrophil and eosinophil infiltration [11].

Dapsone has been successfully used since the 1930s, yet no randomized, controlled, double-blind studies have been performed.

The objective of our study was to determine the efficacy and safety of dapsone in patients with inflammatory skin diseases, treated at the Department of Dermatology of the University Hospital Zurich during the last 20 years.

Methods

For further details, see the supplementary material (for all online supplementary material, see www.karger.com/doi/10.1159/000502256) (Fig. 1).

Table 1. Baseline characteristics

Patients, *n*	175
Male	91
Female	84
Age, years	48.2±17.9 (18–89)
Target dose, number of patients	
25 mg	5
50 mg	20
75 mg	10
100 mg	93
125 mg	2
150 mg	39
200 mg	6
No data	1
Duration of intake, months	11.63±1.5 (0.1–132)
Adherence, *n*	
No signs for poor adherence	154
Poor adherence	21

Age and duration are presented as means ± SD (range).

Results

From 207 patients who received dapsone between 1998 and 2017 in our center, 175 patients met the inclusion criteria. There was a slight male predominance (91 men vs. 84 women). The average age at treatment initiation was 48.2 ± 17.9 years, the youngest patient analyzed was 18, the oldest 89 (Table 1).

The dosage administered ranged from 25 to 200 mg. The daily dose received by the majority of patients (n = 93) was 100 mg. The median duration of dapsone intake was 4 months, the mean 12 ± 20 (0.2–132) months. Poor adherence was documented in 12% (n = 21) of all patients (Table 1).

Thirty-four patients received dapsone for primarily eosinophilic dermatoses, 82 for primarily neutrophilic dermatoses and 59 for "other dermatoses" (Table 2).

Table 2. Diagnosis of patients (*n*) who received dapsone

Primarily eosinophilic dermatoses	34
Urticaria	15
Epidermolysis bullosa acquisita	3
Pemphigus foliaceus	1
Pemphigus vulgaris	4
Mucous membrane pemphigoid	4
Hypereosinophilic dermatitis	2
Relapsing coalescent papular dermatosis of elderly patients	1
Wells' syndrome	4
Primarily neutrophilic dermatoses	82
Bacterial folliculitis	7
Folliculitis decalvans	4
Hidradenitis suppurativa	31
Acne vulgaris and other acne types	4
Acne and hidradenitis suppurativa	4
Akne trias (conglobata, keloidalis nuchae, pectoralis)	1
Dermatitis herpetiformis	9
Subcorneal pustular dermatosis	2
Linear IgA dermatosis	9
Behçet's disease	6
Pyoderma gangrenosum	1
Sweet's syndrome	4
Other dermatoses	59
Livedoid vasculopathy	1
Rosacea	6
Cicatricial alopecia	3
Aphthosis	5
Erythema necrolyticum migrans	1
Strangulation of the upper arm	1
Cheilitis granulomatosa	1
Erythema nodosum	4
Granuloma annulare	3
Necrobiosis lipoidica	2
Perichondritis	1
Sarcoidosis	1
Dermatomyositis	1
Lupus erythematosus	2
Lichen ruber planus, ~ follicularis	2
Perioral dermatitis	1
Reticular erythematous mucinosis	1
IgA pemphigus	1
Erythema elevatum et diutinum	1
Granuloma eosinophilicum faciei	1
Urticarial vasculitis	15
Vasculitis	4

The most common previous systemic treatments included immunosuppressive drugs (*n* = 117), steroids (*n* = 78), antibiotics (*n* = 54) and antihistamines (*n* = 42). Topical steroids were the most prevalent previously used topicals (*n* = 84). In most cases, dapsone was the third line of treatment (*n* = 62). The most common concomitant treatment were systemic steroids (*n* = 45) and topical steroids (*n* = 70; Table 3).

Outcome

After 3 months, 8% (*n* = 14) of all patients reached complete remission and 40.6% (*n* = 71) showed improvement. In 30.3% (*n* = 53) the disease proved to be stable and in 9.1% (*n* = 16) a progression of disease was observed (Fig. 2a). Complete remission was reached in patients with dermatitis herpetiformis (*n* = 3), linear IgA dermatosis (*n* = 3), urticarial vasculitis (*n* = 3), hidradenitis suppurativa (*n* = 2), Wells syndrome (*n* = 1), pyoderma gangrenosum (*n* = 1) and folliculitis decalvans (*n* = 1).

When the last data documented were analyzed, 23 (13.2%) patients showed full remission, 83 (47.4%) improvement of disease, 45 (25.7%) stable disease and 21 (12.0%) progression of disease. No data on outcome were found in 3 (1.7%) cases (Fig. 2b).

There was no statistical difference in outcome regarding the type of disease ($p = 0.0769$; Fig. 3a). Patients who showed remission or improvement after 3 months were significantly older (53 ± 19 vs. 43 ± 15; $p = 0.003$) than patients with stable disease or progression of disease (Fig. 3b). Gender was not associated with treatment response in the first 3 months ($p = 0.9429$; Fig. 3c). Patients who had a remission after 3 months, had used a significantly lower dose of dapsone compared to the improvement group (89.3 ± 45.7 mg vs. 117.3 ± 33.7 mg; $p = 0.006$). Patients, where improvement of symptoms was seen, had significantly higher dosages compared to the group who reported a stable disease (117.3 ± 33.7 vs. 102.8 ± 31.7 mg; $p = 0.0304$). No statistical significance regarding dosage was found in patients who had a stable disease/progression of disease as well as when the remission group/improvement group was compared to the stable disease/progression of disease group ($p = 0.086$; Fig. 3d). The level of methemoglobin was not associated with treatment response in the first 3 months ($p = 0.086$; Fig. 3e).

Safety

Hemolysis was the most common adverse event and seen in 38 patients (21.7%). Common side effects included symptoms of hemolysis (methemoglobinemia). Glucose-6-phosphate dehydrogenase (G6PD) was physiological in 124 patients. In 21 it even occurred to be increased. Only 1 patient was treated despite a decrease in G6PD. No data were available for 31 patients. Hepatopathy (*n* = 20, 11.4%) and nephropathy (*n* = 19, 10.8%) were commonly seen side effects.

In our cohort, and as previously described, we also found patients where transaminases and glomerular fil-

Table 3. Previous and concomitant treatments

Previous systemic treatments, n	
Antibiotics	54
Antimycotics	1
Virostatics	3
Immunosuppressors, total	117
Calcineurin inhibitors	8
Azathioprin	9
Steroids	78
Methotrexate	6
TNF-α inhibitors	1
Hydroxychloroquine	6
Colchicin	8
Mycophenolate	1
Omalizumab	1
Antihistamines	42
Montelukast	8
Retinoids	34
Oral contraception	1
Antiandrogens	3
Zinc	6
Agents with effect on blood and vascular system, total	5
Pentoxifylline	3
Dalteparin	1
Acetylsalicylic acid	1
Hydroxycarbamide	1
No previous systemic treatment	23
No data	7
Previous local treatments, n	
Antibiotics	43
Antimycotics	14
Immunosuppressors, total	94
Calcineurin inhibitors	10
Steroids	84
Benzoyl peroxide	15
Azelaic acid	3
Zinc	6
Phototherapy	11
Agents with effect on blood and vascular system, total	3
Nifedipine	1
Brimonidine	1
Minoxidil	1
No previous local treatment	27
No data	10
Line of treatment, n	
Line 1	10
Line 2	37
Line 3	62
Line 4	38
Line 5	11
Line 6	7
Line 7	2
Line 8	1
No complete data set	7
Systemic combination treatment, n	
Vitamin E	13
Folic acid	3
Antibiotics	6
Immunosuppressors, total	58
Calcineurin inhibitors	2
Azathioprine	3
Steroids	45
Methotrexate	2
Hydroxychloroquine	1
Colchicine	4
Mycophenolate	1
Antihistamines	42
Montelukast	2
Retinoids	12
Oral contraception	1
Antiandrogens	1
Zinc	8
Agents with effect on blood and vascular system, total	4
Pentoxifylline	3
Acetylsalicylic acid	1
No systemic combination treatment	65
No data	1
Local combination treatment, n	
Antibiotics	34
Antimycotics	6
Immunosuppressors, total	80
Calcineurin inhibitors	10
Steroids	70
Benzoyl peroxide	9
Azelaic acid	3
Zinc	5
Phototherapy	3
Laser therapy	3
Agents with effect on blood and vascular system, total	1
Minoxidil	1
No previous local treatment	49
No data	1

tration rate increased [12]. Leukopenia and thrombocytopenia [13], nonspecific interstitial pneumonia and peripheral neuropathy [14] have been described but occurred only in a limited number in our patient cohort (Table 4).

Discussion

In this study, we analyzed the efficacy and safety of dapsone treatment in patients at our center in the last 20 years.

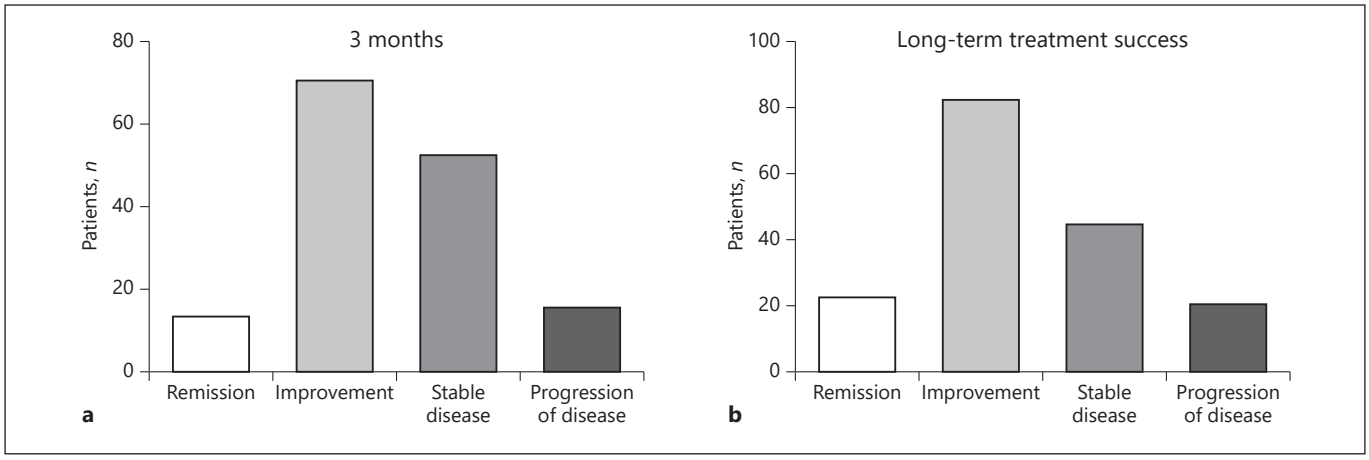

Fig. 2. a Treatment evaluation after 3 months. In the majority of all cases, an improvement under dapsone was seen after 3 months. **b** Long-term treatment success. Treatment response from baseline to the end of therapy was evaluated. In the majority of patients, a beneficial therapeutic response was observed.

In many dermatoses, dapsone is still a standard of treatment, which is supported by our data. In the long term, the majority of all patients had either remission or improvement of disease, emphasizing its high efficacy. This is especially noteworthy, given the fact that dapsone was usually the third line of treatment. It has to be taken into account that our analysis includes data from the last 20 years when dapsone was also used for diagnoses, for which it is not utilized today (e.g., chronic urticaria). Also, off-label treatments were included.

A limitation of our study is the retrospective, monocentric design. Additionally, weight was not routinely documented and therefore not analyzed. Topical use of dapsone (approved in the US for acne vulgaris) was not addressed, as it is not available in Europe. Dapsone can be used for many infectious diseases (leprosy, malaria, actinomycetoma, etc.) [15], but as those patients are rarely seen in Switzerland, we did not have any cases to assess its efficacy in those particular diseases. The wide variety of dermatoses analyzed presents another limitation of this study.

In our real-world data, we did not identify that gender affected treatment outcome. However, older patients significantly showed better responses. The reasons for this observation remain unclear and may be associated with the impact of aging on the immune system. Even though dose escalation in our patients was routinely performed, our overall data did not show a superior treatment response among those receiving a higher dose. Accordingly, even though we did not take the patient's weight into account, a dose escalation beyond 150 mg daily seems unlikely to lead to treatment success.

Overall, dapsone was a safe medication, even though hemolysis was found in 21.7% (never higher than CTC Grade 2) and was in no case the reason for termination of therapy. In most cases patients receive vitamin E to reduce symptoms of methemoglobinemia [16, 17], as it was the case in our cohort. Puavilai et al. [18] show a similar incidence of hemolysis in patients treated with dapsone for leprosy (20%).

Under dapsone, hypersensitivity syndrome (dapsone syndrome) has been reported to develop in approximate-

Fig. 3. Outcomes. * $p < 0.05$, ** $p < 0.01$; ns, nonsignificant. **a** Disease category and outcome. There was no statistical difference whether primarily eosinophilic, neutrophilic or "other" dermatoses were treated ($p = 0.0769$). **b** Age. Patients who showed remission or improvement after 3 months were significantly older than patients who had a stable disease or progression of disease (53 ± 19 vs. 43 ± 15 years; $p = 0.003$). **c** Outcome and gender. There was no significant difference in outcome when stratified for gender ($p = 0.9429$). **d** Outcome and dosage. Patients received dapsone in different dosages (25–200 mg). In the group that showed complete response to treatment, the dosage was lower than compared to the patients where only "improvement" was observed. There was no significant difference in dosage between patients with stable disease and those who progressed under dapsone therapy. **e** Outcome and highest methemoglobin. There was no significant difference between the highest methemoglobin reached and treatment response in the first 3 months ($p = 0.086$).

(For figure see next page.)

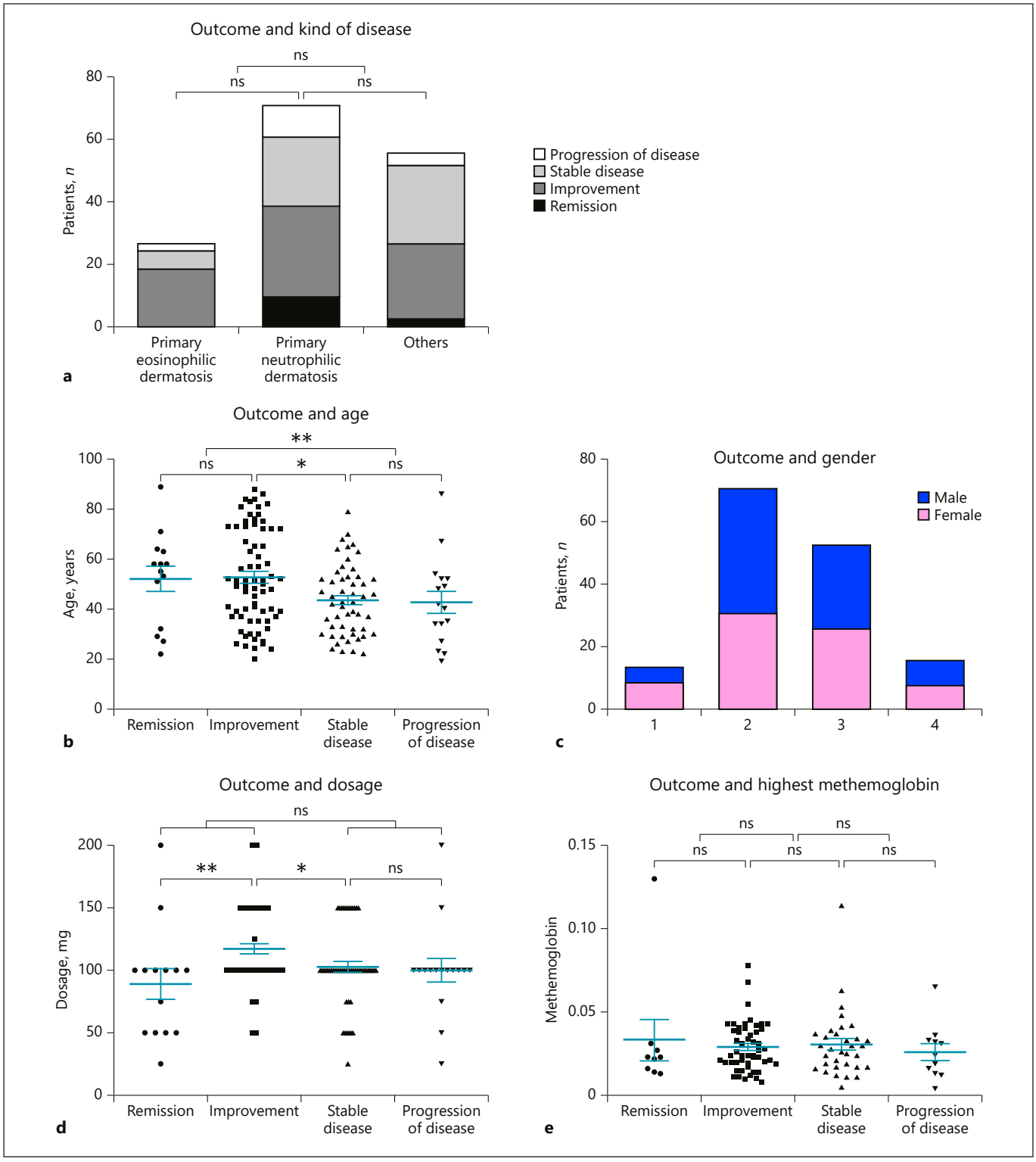

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Table 4. Adverse events under treatment with dapsone

Peripheral neuropathies, *n*	3
No	167
No data	5
Dapsone hypersensitivity syndrome, *n*	4
No	168
No data	3
Nonspecific interstitial pneumonia, *n*	1
No	169
No data	5
Leucopenia, *n*	2
No	156
No data	17
Thrombopenia, *n*	4
No	154
No data	17
Hepatopathy, *n*	20
No	114
No data	41
Nephropathy, *n*	19
No	122
No data	34
Hemolysis, *n*	38
No	106
No data	31
Other adverse events, *n*	
Dyspepsia	23
Diarrhea/obstipation	10
Sleep/concentration/vigilance disorders	4
CNS disorders	6
Change of mood	4
Symptoms of hemolysis/methemoglobinemia	56
Agranulocytosis	1
Increased hematomas	1
Circulation	5
Musculoskeletal system	8
Jaundice	1
Thermoregulation	3
Coughing	2
Influenza-like symptoms	4
Vaginal mycosis	1
Problems with glycemic control	1
Pain in the region of the kidneys, pollakisuria	1
Nonspecific adverse drug reaction	8
Bloated face	2
Drug eruption	4
Photoallergic dermatitis	1
Exitus letalis	1
None	77
Glucose-6-phosphate dehydrogenase, *n*	
Normal	124
Elevated	21
Lowered	1
No data	29

ly 0.5–3.6% of all cases [15]. It is characterized by the clinical triad of fever, rash and systemic involvement (mostly liver and hematological system). It occurs usually between 4 and 6 weeks after drug intake [15]. Fatal outcomes have been reported [12, 19] and mortality is observed in about 9.9% of all hypersensitivity syndrome cases [15]. An association was found with the locus HLA-B*13:01 among leprosy patients [15]. While HLA-B*13:01 is hardly found among Europeans and Africans, it occurs in up to 20% of Asians [15]. In our cohort, 4 patients (2.3%) developed hypersensitivity syndrome, and no fatality occurred.

In summary, our data show that dapsone is a useful and efficient systemic treatment in dermatology. We suggest that daily dosage should be limited up to 150 mg. Even though treatment with dapsone is safe, blood checks ought to be performed regularly to detect hemolysis early. Patients should be informed about hypersensitivity syndrome, and patients of Asian descent profit from screening for HLA-B*13:01.

Key Message

Real-world data show high efficacy and a low number of adverse events.

Statement of Ethics

The authors have no ethical conflicts to declare.

Disclosure Statement

All authors have no conflict of interest.

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References

1 Wozel G, Blasum C. Dapsone in dermatology and beyond. Arch Dermatol Res. 2014 Mar; 306(2):103–24.
2 Buttle GS, Smith S. The treatment of streptococcal infections in mice with 4:4′-diaminodiphenyl sulfone. Lancet. 1937;1(5936):1331–4.
3 E Fourneau JT, F Nitti, et al. Action antistreptococcique des derives sulfures organiques. Compt Rendu Acad Sci. 1937;204 1763–66.

4 Zuidema J, Hilbers-Modderman ES, Merkus FW. Clinical pharmacokinetics of dapsone. Clin Pharmacokinet. 1986 Jul-Aug;11(4):299–315.
5 Sanders SW, Zone JJ, Foltz RL, Tolman KG, Rollins DE. Hemolytic anemia induced by dapsone transmitted through breast milk. Ann Intern Med. 1982 Apr;96(4):465–6.
6 Branski D, Kerem E, Gross-Kieselstein E, Hurvitz H, Litt R, Abrahamov A. Bloody diarrhea—a possible complication of sulfasalazine transferred through human breast milk. J Pediatr Gastroenterol Nutr. 1986 Mar-Apr;5(2):316–7.
7 Lowe J. Studies in sulphone therapy. Lepr Rev. 1952 Jan;23(1):4–29.
8 Żychowska M. Dapsone: a forgotten and underestimated treatment option for bullous pemphigoid? Br J Dermatol. 2017 Nov;177(5):1156–7.
9 Bolotin D, Petronic-Rosic V. Dermatitis herpetiformis. Part II. Diagnosis, management, and prognosis. J Am Acad Dermatol. 2011 Jun;64(6):1027–33.
10 Lindhaus C, Elsner P. Granuloma Faciale Treatment: A Systematic Review. Acta Derm Venereol. 2018 Jan;98(1):14–8.
11 Holm JG, Ivyanskiy I, Thomsen SF. Use of nonbiologic treatments in antihistamine-refractory chronic urticaria: a review of published evidence. J Dermatolog Treat. 2018 Feb;29(1):80–97.
12 Lorenz M, Wozel G, Schmitt J. Hypersensitivity reactions to dapsone: a systematic review. Acta Derm Venereol. 2012 Mar;92(2):194–9.
13 Kobe Y, Setoguchi D, Kitamura N. Dapsone-induced agranulocytosis leading to perianal abscess and death: a case report. J Med Case Reports. 2011 Mar;5(1):107.
14 Guragain S, Upadhayay N, Bhattarai BM. Adverse reactions in leprosy patients who underwent dapsone multidrug therapy: a retrospective study. Clin Pharmacol. 2017 Jun;9:73–8.
15 Doherty N, Powell E. Effects of age and years of exposure on the economic benefits of fluoridation. J Dent Res. 1974 Jul-Aug;53(4):912–4.
16 Collin P, Reunala T. Recognition and management of the cutaneous manifestations of celiac disease: a guide for dermatologists. Am J Clin Dermatol. 2003;4(1):13–20.
17 Nicolas ME, Krause PK, Gibson LE, Murray JA. Dermatitis herpetiformis. Int J Dermatol. 2003 Aug;42(8):588–600.
18 Puavilai S, Chutha S, Polnikorn N, Timpatanapong P, Tasanapradit P, Charuwichitratana S, et al. Incidence of anemia in leprosy patients treated with dapsone. J Med Assoc Thai. 1984 Jul;67(7):404–7.
19 Pai S, Munshi R, Nayak C. Fatal dapsone hypersensitivity syndrome with hypothyroidism and steroid-induced diabetes mellitus. Indian J Pharmacol. 2017 Sep-Oct;49(5):396–8.